REMARKS

Interview request

Applicants respectfully request a telephonic interview after the Examiner has reviewed the instant response and amendment. Applicants request the Examiner call Applicants' representatives David Devernoe at 858 720 7943 or Gregory Einhorn at (858) 720-5133.

Status of the Claims

Pending claims

Claims 1-18, 47-48, 74-89, 92-93, 102-108, 112-116 and 118-121 are pending.

Claims added and canceled in the instant amendment

In the present response, claims 5, 12, 18, 81-83 and 87 are canceled, without prejudice or disclaimer. Claims 122 and 123 are added herein. Thus, after entry of the instant amendment, claims 1-4, 6-12, 14-17, 47-48, 74-80, 84-86, 88-89, 92-93, 102-108, 112-116 and 118-124 will be pending and under examination.

Both before and after the above changes and cancellations, and the addition of new claims, the invention was described in full, clear, concise, and exact terms and met all conditions for patentability under 35 USC 101 *et seq.* The scope of the claims of any resulting patent (and any and all limitations in any of said claims) shall not under any circumstances be limited to their literal terms, but are intended to embrace all equivalents.

Renumbered Claims

The Office has indicated that the numbering of the claims is not in accordance with 37 C.F.R. § 1.126. Specifically, the Office has indicated that two claims are presented having the number designation "75." As such, the Office has indicated that the second claim 75 and claims previously numbered 76-120 have been renumbered as claims 76 and 77-121. Moreover, the Office indicated that each reference to claim numbers in the present Office action refer to the claims as renumbered.

The Applicants thank the office for the careful reading of the pending claims and herein maintain the claim numbering as renumbered by the Office. The present amendment incorporates amendments to renumbered claims 76-89, 92-93, 105, 107 and 119-120 solely for

PAGE 21/60 * RCVD AT 8/20/2004 9:23:39 PM [Eastern Daylight Time] * SVR:USPTO-EFXRF-1/1 * DNIS:8729306 * CSID:8587205125 * DURATION (mm-ss):25-38

purposes limited to updating dependency of claims due to the renumbering by the Office. It is believed that the present amendments to these claims merely clarify certain aspects of the present invention and, as these amendments are not made for reasons related to patentability, they do not narrow the intended scope of the claims.

Outstanding Rejections

Claims 75-89, 92 and 106 are rejected under 35 U.S.C. §112, second paragraph. Claims 1-5, 7-18, 47-48, 75-89, 92, 93 and 102-107 are rejected under 35 U.S.C. §112, first paragraph (written description). Claims 1-18, 47-48, 74-89, 92, 93 and 102-108, 112-116 and 118-120 are rejected under 35 U.S.C. §112, first paragraph (enablement). Claims 1, 2, 4, 5, 7-14, 16-18, 47, 48, 75-87, 92 and 102 to 107, are rejected under 35 U.S.C. §102(b). Claims 88 and 89 are rejected under 35 U.S.C. §103(a). Applicants respectfully traverse all outstanding objections to the specification and rejection of the claims.

Support for Claim Amendments

Support for the new and amended claims can be found throughout the application for the skilled artisan. For example, support for claims directed to nucleic acids and polypeptides of the invention of various lengths and identities can be found, inter alia, in paragraph 74, page 17; paragraphs 201 to 203, pages 50 to 51; paragraphs 237-239, pages 60-61; paragraphs 251-252, pages 64-66, of the specification. Applicants submit that no new matter is introduced by the present amendments.

Claim Objections

Claim 4 is objected to for allegedly failing to further limit the subject matter of the claim from which it depends. The Office alleges that the recitation of the formula in claim 4 does not add anything to the recitation of the T_m in claims 2 and 3 as it merely recites the known formula for calculating the T_m of a nucleic acid. Although the Applicants agree that a known formula is recited in claim 4, this formula is not the only known formula for determining melting temperature. See, e.g., Current Protocols in Molecular Biology 2.10.8 (Supp. 66, April 2004) (citing the equation of Meinkoth & Wahl (1984)) (enclosed herewith as Exhibit A). As such, this claim further limits

PAGE 22/60 * RCVD AT 8/20/2004 9:23:39 PM [Eastern Daylight Time] * SVR:USPTO-EFXRF-1/1 * DNIS:8729306 * CSID:8587205125 * DURATION (mm-ss):25-38

claims 2 or 3, as a particular melting temperature formula (amongst the many known in the art) is recited.

Issues under 35 U.S.C. §112, second paragraph

Claims 75-89, 92 and 106 stand rejected under 35 U.S.C. §112, second paragraph, for allegedly being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicants regard as the invention.

The instant amendment addresses the 35 U.S.C. §112, second paragraph issues discussed in the Office action.

Issues under 35 U.S.C. §112, first paragraph

Written Description

Claims 1-5, 7-18, 47-48, 75-89, 92, 93 and 102-107 stand rejected under 35 U.S.C. §112, first paragraph, as allegedly containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the art that the inventors, at the time the application was filed, had possession of the claimed invention.

The Office alleges that the Applicants' previous argument was not commensurate with the scope of the pending claims as claims 2-4, 17, 18, 47, 75-89, 92 and did not contain any functional limitations. The present amendment addresses this issue.

With regard to claims 1, 5, 7-18, 47-48, 75-89, 92-93 and 102-107, the Office alleges these claims fail to recite "sufficient structural limitations." The Office specifically indicates that the rejected claims:

> recite nucleic acids which comprise only 35-500 residues having 85% identity to a portion of SEQ ID NO:125 (claims 1, 5, 7-13, 16 and 102-107), or only 100 residues having 90% or 95% identity to a portion of SEQ ID NO:125 (Claims 14 and 15) as the only recited structural limitations of the claims. These recited structural features of the genus do not constitute a substantial portion of the genus as the remainder of the structure of a nucleic acid encoding a polypeptide with alpha amylase activity is completely undefined. Fragments consisting of only 35-500 residues having 85% identity to a portion of SEQ ID NO:125 or only 100 residues having 90% or 95% identity to a portion of SEQ ID NO:125 are highly unlikely to have alpha amylase activity . . ..

The Applicants respectfully traverse.

PAGE 23/60 * RCVD AT 8/20/2004 9:23:39 PM [Eastern Daylight Time] * SVR:USPTO-EFXRF-1/1 * DNIS:8729306 * CSID:8587205125 * DURATION (mm-ss):25-38

"The written description requirement does not require the applicant to describe exactly the subject matter claimed, instead the description must clearly allow persons of ordinary skill in the art to recognize that he or she invented what is claimed." *Moba, B.V. v. Diamond Automation, Inc.*, 325 F.3d 1306, 1321 (Fed. Cir. 2003) (citation omitted). As such, the original disclosure need not provide *in haec verba* support for the claimed subject matter. *See Fujikawa v. Wattanasin*, 39 USPQ2d 1895, 1904 (Fed. Cir. 1996). The threshold aspect if that one of skill in the art must be able to recognize that the Applicants demonstrated possession of the claimed invention. The Applicants respectfully submit that the Examples, methods and materials provided in the specification provide such a description for the claimed subject matter. The sequences encompassed by the present claims are defined via shared physical and structural properties in terms that convey with reasonable clarity to those skilled in the art that Applicants, as of the filing date and at the time of the invention, were in possession of the claimed invention.

With respect to satisfying the written description requirement for alpha amylases, and nucleic acids encoding alpha amylases, having sequences having a sequence identity (e.g., 90%, 95%, 97% or 99%) to the sequences as set forth in SEQ ID NOs:125 and 126, Applicants respectfully refer to the USPTO Revised Interim Guidelines concerning compliance with the written description requirement of U.S.C. §112, first paragraph. In example 14 of the written description guidelines (a copy submitted as Exhibit A in Applicants' February 24, 2004 response), a claim reciting variants claimed by sequence identity to a sequence is sought (specifically, "A protein having SEQ ID NO:3 and variants thereof that are at least 95% identical to SEQ ID NO:3 and catalyze the reaction of A → B). In the example, the specification is described as providing SEQ ID NO:3 and a function for the protein. The specification contemplates, but does not exemplify variants of SEQ ID NO:3 that can have substitutions, deletions, insertions and additions. Procedures for making proteins with substitutions, deletions, insertions, and additions are routine in the art and an assay is described which will identify other proteins having the claimed activity. The analysis of example 14 states that procedures for making variants (which have 95% sequence identity) are conventional in the art. The written description guidelines' conclusion states that the disclosure meets the requirements of 35 U.S.C. §112, first paragraph, as providing adequate written description for the claimed invention. The written description guidelines do not require description

PAGE 24/60 * RCVD AT 8/20/2004 9:23:39 PM [Eastern Daylight Time] * SVR:USPTO-EFXRF-1/1 * DNIS:8729306 * CSID:8587205125 * DURATION (mm-ss):25-38

of any structural features (other than the % sequence identity limitation) to satisfy the written description requirement of section 112.

Analogously, the nucleic acid and amino acid sequences of the present claims are described by structure (the exemplary nucleic acid (SEQ ID NO:125) and polypeptide (SEQ ID NO:126)), a physico-chemical property (percent sequence identity or stringent hybridization) and function (alpha amylase activity). The claimed genus of polypeptides all must have, or encode a polypeptide having, alpha amylase activity and a specific sequence identity (e.g., 90%, 95%, 97% or 99%) to SEQ ID NO:125 or 126, or, hybridize under stringent conditions to an exemplary nucleic acid. The Guidelines recognize that the written description requirements are met for a genus of polypeptides described by structure, a physico-chemical property (e.g., a % sequence identity, stringent hybridization) and a defined function, the genus of claimed polypeptides also meet the written description requirements of section 112.

With specific regard to the hybridization claim (claims 92), the Applicants direct the Office's attention to Example 9 of the Written Description Guidelines. *See* 66 Fed. Reg. 1099 (2001) ("Example 9") (attached hereto as Exhibit B). Example 9 describes a situation involving a claim to a genus of nucleic acids that specifically hybridize (under highly stringent conditions) to the complement of a specifically described sequence (SEQ ID NO:1). In Example 9, SEQ ID NO:1 was disclosed in the specification, which encoded a protein having a known function. In addition, an example was provided in the specification involving the use of the complement of SEQ ID NO:1 to isolate nucleic acids via hybridization. These isolated nucleic acids were not sequenced, however, they were expressed and "several" were shown to encode proteins having activity similar to SEQ ID NO:1. A single species was disclosed within the scope of the claimed genus comprising a molecule consisting of SEQ ID NO:1. The relevant art indicated that hybridization techniques using known DNA as a probe under highly stringent conditions were conventional in the art.

Example 9, however, is silent with regard to the number and percentage of sequences that did not encode proteins having activity similar to SEQ ID NO:1. Moreover, Example 9 is silent with regard to the percent identity the nucleic acids shared with SEQ ID NO:1. This Guideline indicates that adequate written description was provided based on the use of hybridization language, the "encoding function" of DNA, and the level of skill in the art. The Guidelines indicate that

PAGE 25/60 * RCVD AT 8/20/2004 9:23:39 PM [Eastern Daylight Time] * SVR:USPTO-EFXRF-1/1 * DNIS:8729306 * CSID:8587205125 * DURATION (mm-ss):25-38

importation of specific hybridization conditions (which describe the particulars of the high stringency hybridization) into the claim text is not required to meet the written description requirements. These written description guidelines, of course, are illustrative of the numerous potential written description issues encountered by the Office, and numerous analogous and acceptable variations of the examples set out in the Guidelines surely exist.

Applicants respectfully aver that the present hybridization claims are sufficiently analogous to Example 9 of the written description guidelines to indicate that the instant claims meet the written description requirements. The structure of SEQ ID NO:125 and the function of the encoded protein are described in the specification. The disclosure clearly contemplates the isolation (via hybridization) of nucleic acids that encode proteins having alpha amylase activity using the described sequence, even if these nucleic acids are less than 100% identical to SEQ ID NO:125. Moreover, both Example 9 of the Guidelines and the present claims set forth claims that define a genus of claimed nucleic acids by the hybridization condition limitation (highly stringent conditions). Similar to Example 9, the level of skill in the art is high, and an artisan would understand hybridization techniques in accordance with the materials and limitations provided in the claims. Further, both Example 9 and the present claims include clauses that limit the hybridizing nucleic acid in terms of the function of the protein that it encodes.

The instant amendment also addresses the Examiner's concerns regarding stringent hybridization conditions.

Accordingly, the claims fully comply with the requirements for written description of a genus of nucleic acids as set forth in *University of California v. Eli Lilly & Co.*, 43 USPQ2d 1398 (Fed. Cir. 1997). As noted above, the instant claims clearly set forth specific structural and physical characteristics of the claimed amylase-encoding nucleic acids. The claimed genus of polypeptides all must have amylase activity and a specific physical characteristic, e.g., a % sequence identity or stringent hybridization to the exemplary nucleic acid or polypeptide.

Enablement

Claims 1-18, 47-48, 74-89, 92, 93 and 102-108, 112-116 and 118-120 are rejected under 35 U.S.C. §112, first paragraph, because the specification allegedly does not reasonably provide enablement for the claimed invention.

PAGE 26/60 * RCVD AT 8/20/2004 9:23:39 PM [Eastern Daylight Time] * SVR:USPTO-EFXRF-1/1 * DNIS:8729306 * CSID:8587205125 * DURATION (mm-ss):25-38

The Patent Office notes that the specification is enabling for polynucleotides encoding SEQ ID NO:126.

The Patent Office remains concerned that because there is a large number of variants that fall within the scope of the claimed nucleic acids, it might take undue experimentation to create the variants and test them for activity.

To address this concern, the present amendment incorporates claim amendments that increase both the sequence identity and fragment length of the nucleic acids and polypeptides encompassed therein.

However, Applicants respectfully maintain that whether large numbers of compositions (e.g., variants of nucleic acids or proteins) must be screened to determine if one is within the scope of the claims is irrelevant to an enablement inquiry; please see Applicants response of February 24, 2004, e.g., page 35. Enablement is not precluded by the necessity to screen large numbers of compositions, as long as that screening is "routine," i.e., not "undue," to use the words of the Federal Circuit. Hybritech, Inc. v. Monoclonal Antibodies, Inc., 802 F.2d 1367, 1384, 231 USPQ 81, 94 (Fed. Cir. 1986), cert. denied, 480 U.S. 947 (1987). "Time and difficulty" are not determinative of undue experimentation if the experimentation is routine. See PPG Indus., Inc. v. Guardian Indus. Corp., 75 F.3d 1558, 1564, 37 USPQ2d 1618, 1623 (Fed. Cir. 1996). In Hybritech, Inc., the court was acknowledging that, because practitioners in that art are prepared to screen large numbers of negatives in order to find a sample that has the desired properties, the screening that would be necessary to make additional antibody species was not "undue experimentation." In Hybritech, Inc., the court acknowledged that, using 1980's technology, this was not "undue experimentation."

Analogously, practitioners in the art at the time of this invention were prepared to make and screen large numbers of negatives in order to find a sample with the desired properties, e.g., an amylase-encoding nucleic acid. Those skilled in the relevant art at the time of the instant claimed invention could, using the state of the art and Applicants' written disclosure, produce and screen a genus of nucleic acids (e.g., nucleic acids having 90%, 95%, 97% or 99% sequence identity to SEQ ID NO:125) for alpha amylase activity without undue experimentation. Thus, the making

PAGE 27/60 * RCVD AT 8/20/2004 9:23:39 PM [Eastern Daylight Time] * SVR:USPTO-EFXRF-1/1 * DNIS:8729306 * CSID:8587205125 * DURATION (mm-ss):25-38

and screening that would be necessary to generate alpha amylase-encoding nucleic acids, as set forth in the claimed methods, was not "undue experimentation."

Regarding making the claimed genus of nucleic acids, Applicants respectfully aver that the specification did provide the skilled artisan a reasonable amount of guidance. For example, in paragraph [0079], page 19, the specification provides guidance on alternative methods for generating the claimed genus of nucleic acids. One such protocol, Gene Site Saturation Mutagenesis™ (GSSM™), is described in detail, e.g., in paragraphs [0162] to [0174] pages 40 to 43. GSSM™ involves use of codon primers (containing a degenerate N,N,N sequence) to introduce point mutations into a polynucleotide, so as to generate a set of progeny polypeptides in which a full range of single amino acid substitutions is represented at each amino acid position. See also, Example 3, on page 87, and Example 10, pages 105 to 109, of the specification, describing gene optimization and amylase ligation reassembly, respectively. Additionally, the Patent Office acknowledges that creation of nucleic acids having the structural limitations recited in the claims was routine in the art (please note page 10, lines 16 to 18, of the final Office action).

However, the Patent Office remains concerned that testing an extremely large number of variants encompassed by the claims may be undue experimentation. The Patent Office is concerned that because, inter alia, there is no guidance or knowledge as to which are the structural elements in the polypeptide encoded by the exemplary nucleic acid that correlate with enzyme activity (see, e.g., the paragraph spanning pages 10 and 11 of the office action), it would be undue experimentation to test an "extremely large number of variants" to determine if a nucleic acid encoded an amylase and was within the scope of the claimed invention.

Applicants respectfully maintain that the specification did provide the skilled artisan a reasonable amount of guidance with respect to screening for amylases, i.e., screening variant nucleic acids to identify the claimed genus of amylase-encoding nucleic acids. For example, Example 1, pages 83 to 84, describes a protocol to identify and characterize thermostable amylases; Example 2, pages 84 to 86, and Example 4, page 87, describe protocols to identify and characterize thermostable amylases at alkaline pH; Example 5, pages 87 to 89, and Example 6, pages 90 to 93, Example 7, pages 94 to 103, describe exemplary amylase activity assays; and, Example 9, page 105, describes a protocol to determine the pH optimum for an amylase activity (the hydrolysis of starch).

PAGE 28/60 * RCVD AT 8/20/2004 9:23:39 PM [Eastern Daylight Time] * SVR:USPTO-EFXRF-1/1 * DNIS:8729306 * CSID:8587205125 * DURATION (mm-ss):25-38

Accordingly, the specification provides guidance on alternative, routine protocols for determining alpha amylase activity that can be practiced without undue experimentation.

Furthermore, as declared by Dr. Short in the declaration submitted in Applicants' previous response, the state of the art at the time of the invention and the level of skill of the person of ordinary skill in the art, e.g., screening enzymes, and nucleic acids encoding enzymes, for various amylase activities, e.g., alpha amylase activity, was very high. Dr. Short declared that using the teaching of the specification (see discussion, above), one skilled in the art could have selected routine methods known in the art at the time of the invention to express variants of nucleic acids encoding the exemplary amylase of the invention and screen them for expression of polypeptides having various amylase activities. Dr. Short declared that while the numbers of samples needed to be screened may have been high, the screening procedures were routine and successful results predictable (i.e., it was predictable to find nucleic acids encoding amylases having various activities).

In the enclosed Declaration, Dr. Short declares that at the time of the invention, high through-put *in vivo* (e.g., whole cell) and *in vitro* nucleic acid expression and enzyme (amylase) screening protocols were well known in the art, and using these high through-put screening assays with amylase assays known in the art, including those routine amylase screening assays described in the specification (see discussion, above), one of skill in the art could have routinely expressed variant nucleic acids and routinely identified amylase-encoding nucleic acids, i.e., screened for and identified the claimed genus of amylase-encoding nucleic acids without undue experimentation. Accordingly, it would not have taken undue experimentation to make and use the claimed invention, including screening for and identifying the claimed genus of amylase-encoding nucleic acids.

The Patent Office also remains concerned that, inter alia, the specification does not establish regions of protein structure which may be modified while producing variants having alpha amylase activity. It was alleged that in the absence of any information as to how structure correlates with function, one of skill in the art would have to go through the burden of undue experimentation to isolate or make the claimed nucleic acids. It was alleged that the specification is silent in regard to which are the amino acid residues with can be substituted, deleted or inserted into a nucleic acid to obtain structural, and functional, homologues.

sd-215892

However, Applicants respectfully note that the specification does provide guidance as to what amino acid substitutions can be made to make the genus of amylases of the invention. For example, paragraph 0075, on pages 17 to 18 of the specification, teaches

> ... a "substantially identical" amino acid sequence is a sequence that differs from a reference sequence by one or more conservative or non-conservative amino acid substitutions, deletions, or insertions, particularly when such a substitution occurs at a site that is not the active site of the molecule, and provided that the polypeptide essentially retains its functional properties. A conservative amino acid substitution, for example, substitutes one amino acid for another of the same class (e.g., substitution of one hydrophobic amino acid, such as isoleucine, valine, leucine, or methionine, for another, or substitution of one polar amino acid for another, such as substitution of arginine for lysine, glutamic acid for aspartic acid or glutamine for asparagine). One or more amino acids can be deleted, for example, from an alpha amylase polypeptide, resulting in modification of the structure of the polypeptide, without significantly altering its biological activity. For example, amino- or carboxyl-terminal amino acids that are not required for alpha amylase biological activity can be removed. Modified polypeptide sequences of the invention can be assayed for alpha amylase biological activity by any number of methods, including contacting the modified polypeptide sequence with an alpha amylase substrate and determining whether the modified polypeptide decreases the amount of specific substrate in the assay or increases the bioproducts of the enzymatic reaction of a functional alpha amylase polypeptide with the substrate.

Accordingly, the specification did provide guidance as to what amino acid changes could be made to make the genus of claimed amylases. Furthermore, Applicants respectfully aver that direction to the skilled artisan as to which amino acid residues can be substituted, deleted or inserted into a nucleic acid to obtain structural, and functional, homologues of an enzyme could also be found in the art at the time of the invention. For example, the three dimension structure of amylases had been described, see, e.g., Machius (1995) J. Mol. Biol. 246(4):545-549; Kadziola (1994) J. Mol. Biol. 239:104-121, thus providing direction as to which amino acid residues can be modified and how structure correlates with function. Furthermore, at the time of the invention one of skill in the art would have been aware of the many studies of amylase activity and active sites, see, e.g., Matsui (1994) Biochemistry 33(2):451-458, "Roles of the aromatic residues conserved in the active center of *Saccharomycopsis* alpha-amylase for transglycosylation and hydrolysis activity;" Matsui (1991) Biochim. Biophys. Acta. 1077(3):416-419, "An increase in the transglycosylation activity of Saccharomycopsis alpha-amylase altered by site-directed

PAGE 30/60 * RCVD AT 8/20/2004 9:23:39 PM [Eastern Daylight Time] * SVR:USPTO-EFXRF-1/1 * DNIS:8729306 * CSID:8587205125 * DURATION (mm-ss):25-38

mutagenesis." Accordingly, one skilled in the art at the time of the invention, using the teaching of the specification (and including the teaching of the specification), had many sources of direction to determine which amino acid residues could be substituted, deleted or inserted into a nucleic acid to obtain structural, and functional, homologues of an enzyme.

However, Applicants respectfully aver that it would not have been necessary for one skilled in the art to understand which specific regions of amylase structure could be modified to generate the genus of nucleic acids or polypeptides of the invention. As noted by Dr. Short in his previously submitted Rule 132 declaration, it would not have required any knowledge or guidance as to which are the specific structural elements, e.g., amino acid residues, that correlate with amylase activity to create variants of the exemplary nucleic acid and test them for the expression of polypeptides or peptides having amylase activity.

In the enclosed expert declaration, Dr. Short declares that it would not have been necessary for the skilled artisan to understand which specific regions or structural elements of an amylase were necessary for function or activity to routinely generate the genus of claimed amylase-encoding nucleic acids. Dr. Short declares that methods for making and screening enzymes were sufficiently comprehensive and routine at the time of the invention to predictably generate a genus of amylase-encoding sequences without need of knowing which specific regions or structural elements of a sequence or structure affected function or activity. Dr. Short declares that methods known at the time of the invention for modifying nucleic acid and polypeptide sequences in combination with high through-put enzyme (amylase) screening made methods that required previous knowledge of structural elements necessary for enzymatic activity obsolete and unnecessary. Dr. Short declares that high through-put enzyme screening methodologies known at the time of the invention (including *in vivo* and *in vitro* nucleic acid expression and enzyme (amylase) screening protocols) made methods that require previous knowledge of protein structure, including secondary or tertiary structure, active site sequences, and the like obsolete and unnecessary. Dr. Short declares that by using methods known in the art at the time of the invention, including the amylase screening protocols described in the specification, it would not have been necessary to understand which specific regions of amylase structure needed to be modified to generate the claimed genus of nucleic acids without undue experimentation. Dr. Short declares that

PAGE 31/60 * RCVD AT 8/20/2004 9:23:39 PM [Eastern Daylight Time] * SVR:USPTO-EFXRF-1/1 * DNIS:8729306 * CSID:8587205125 * DURATION (mm-ss):25-38

the specification provided sufficient guidance to one of ordinary skill in the art to make and use the genus of amylase-encoding nucleic acids to practice the methods of the invention.

The Patent Office cites art purportedly showing the "unpredictability of assigning function based on structural homology and how small changes can lead to major changes in function." Please see the Office action, e.g., page 9, citing Bork (2000) Genome Res. 10:398-400; Broun et al. (1998) Science 282:1315-1317; Van de Loo et al. (1995) Proc. Natl. Acad. Sci. USA 92:6743-6747; Witkowski et al. (1999) Biochemistry 38:11643-11650; and Seffernick et al. (2001) J. of Bacteriol. 183:2405-2410.

In order to make a rejection, the examiner has the initial burden to establish a reasonable basis to question the enablement provided for the claimed invention. In re Wright, 999 F.2d 1557, 1562, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993) (examiner must provide a reasonable explanation as to why the scope of protection provided by a claim is not adequately enabled by the disclosure). A specification disclosure which contains a teaching of the manner and process of making and using an invention in terms which correspond in scope to those used in describing and defining the subject matter sought to be patented must be taken as being in compliance with the enablement requirement of 35 U.S.C. 112, first paragraph, unless there is a reason to doubt the objective truth of the statements contained therein which must be relied on for enabling support. As stated by the court, "it is incumbent upon the Patent Office, whenever a rejection on this basis is made, to explain why it doubts the truth or accuracy of any statement in a supporting disclosure and to back up assertions of its own with acceptable evidence or reasoning which is inconsistent with the contested statement. Otherwise, there would be no need for the applicant to go to the trouble and expense of supporting his presumptively accurate disclosure." In re Marzocchi, 439 F.2d 220, 224, 169 USPQ 367, 370 (CCPA 1971). See also MPEP §2164.04, rev. 2, May 2004, pg 2100-189.

The examiner must weigh all the evidence before him or her, including the specification and any new evidence supplied by applicant with the evidence and/or sound scientific reasoning previously presented in the rejection and decide whether the claimed invention is enabled. The examiner should never make the determination based on personal opinion. The determination should always be based on the weight of all the evidence. MPEP §2164.05, 8th edition, rev. 2, May 2004, pg 2100-190 to -191.

sd-215892

Applicants respectfully aver that the examiner has not met his or her initial burden to establish a reasonable basis to question the enablement provided for the claimed invention, and specifically address, below, how the art used to support the Office's enablement rejection is not sufficient to rebut the presumptively enabled specification.

Additionally, because the examiner must weigh all the evidence before him or her, the Office did not sufficiently consider and specifically address Dr. Short's previously submitted Rule 132 expert declaration regarding enablement, in which Dr. Short declared, inter alia, it would not have required any knowledge or guidance as to which are the specific structural elements, e.g., amino acid residues, that correlate with amylase activity to create variants of the exemplary nucleic acid and test them for the expression of polypeptides or peptides having amylase activity, with reasons to doubt the objective truth of the statements contained therein. Applicants respectfully aver that their arguments, and Dr. Short's expert declaration, are sufficient to rebut any possible *prima facie* case of lack of enablement, i.e., Applicants have presented persuasive arguments that one skilled in the art would be able to make and use the claimed invention using the application as a guide. The evidence provided by applicant need not be conclusive but merely convincing to one skilled in the art. MPEP 2164.05, 8th edition, rev. 2, May 2004, pg 2100-190 to -191.

As noted above, the Patent Office cited Bork, Broun et al., Van de Loo et al., Witkowski et al. and Seffernick et al. to show the "unpredictability of assigning function based on structural homology and how small changes can lead to major changes in function." However, none of these references, individually or in their totality, are sufficient to rebut the presumption of enablement. None of these references are directed to whether, or not, screening a large number of nucleic acid variants (of an exemplary nucleic acid of the invention) would have constituted undue experimentation to one skilled in the art at the time of the invention.

Bork (2000) Genome Res. 10:398-400, discusses limits on computational sequence analysis. In Bork, there is no discussion regarding the merits or difficulties of protocols that screen for enzyme activity, e.g., screen for enzyme activity in a library of polypeptides expressed by a plurality of nucleic acid variants. Bork only questions the accuracy of assigning protein function based on sequence identity. However, the amylase activity of polypeptides of the instant invention are not based on sequence identity homology to known proteins, but rather are based on empirical,

PAGE 33/60 * RCVD AT 8/20/2004 9:23:39 PM [Eastern Daylight Time] * SVR:USPTO-EFXRF-1/1 * DNIS:8729306 * CSID:8587205125 * DURATION (mm-ss):25-38

experimental data demonstrating that polypeptides of the invention have amylase activity (see, e.g., Example 1, page 83, of the specification). Interestingly, Bork opines that most computational sequence analysis methodologies can predict function with an expected accuracy of about 70%.

Broun et al. (1998) Science 282:1315-1317, shows that a small number of amino acid reside changes in the catalytic site of a family of structurally related enzymes can result in a change in activity (in particular, Broun found that as few as four amino acid substitutions can convert an oleate 12-desaturase to a hydroxylase and as few as six result in conversion of a hydroxylase to a desaturase). However, in Broun, there is no discussion regarding the merits or difficulties of protocols that screen for enzyme activity, e.g., screen for enzyme activity in a library of polypeptides expressed by a plurality of nucleic acid variants. In fact, it appears that Broun considered screening for enzyme activity in their enzyme variants a routine process. There is no discussion on whether changes in non-catalytic site amino acid residues have any effect on enzyme activity. In fact, Broun's data suggest that most changes in an enzyme's amino acid sequence (e.g., non-catalytic site amino acid residues) are not important in determining, or changing, its catalytic specificity.

Van de Loo et al. (1995) Proc. Natl. Acad. Sci. USA 92:6743-6747, prepared a cDNA library from a castor-oil plant, obtained partial nucleotide sequences for 468 anonymous clones, identified several cDNA clones encoding a polypeptide of 387 amino acids with a predicted MW of 44,407 and with approximately 67% sequence homology to an oleate desaturase, and expressed a full-length clone in a transgenic tobacco, which resulted in the accumulation of low levels of 12-hydroxyoleic acid in seeds, indicating that the expressed clone encodes an oleate hydroxylase. Van de Loo opined that these results suggested that fatty acyl desaturases and hydroxylases share similar reaction mechanisms. However, in Van de Loo, there is no discussion regarding the merits or difficulties of protocols that screen for enzyme activity, e.g., screen for enzyme activity in a library of polypeptides expressed by a plurality of nucleic acid variants. In fact, it appears that Van de Loo considered screening for enzyme activity in their single expressed clone a routine process. Van de Loo also credited the high-throughput capabilities of automated DNA sequenators in the examination of their anonymous clones.

PAGE 34/60 * RCVD AT 8/20/2004 9:23:39 PM [Eastern Daylight Time] * SVR:USPTO-EFXRF-1/1 * DNIS:8729306 * CSID:8587205125 * DURATION (mm-ss):25-38

Witkowski et al. (1999) Biochemistry 38:11643-11650, also showed that a small number of amino acid reside changes in the catalytic site of a family of structurally related enzymes can result in a change in activity. Witkowski noted that beta-ketoacyl synthases involved in the biosynthesis of fatty acids and polyketides exhibit extensive sequence similarity and share a common reaction mechanism. Interestingly, Witkowski also noted that multiple sequence alignments identified catalytic sites and provided the first clues about the possible identities of residues that play critical roles in catalysis. In fact, as with Broun, Witkowski's data suggest that most changes in an enzyme's amino acid sequence (e.g., non-catalytic site amino acid residues) are not important in determining, or changing, its catalytic specificity. In Witkowski, there is no discussion regarding the merits or difficulties of protocols that screen for enzyme activity, e.g., screen for enzyme activity in a library of polypeptides expressed by a plurality of nucleic acid variants. It appears that Witkowski considered screening for enzyme activity a routine process.

Seffernick et al. (2001) J. of Bacteriol. 183:2405-2410, also shows that a small number of amino acid reside changes in the catalytic site of an enzyme can result in a change in activity. Seffernick compared a deaminase (melamine deaminase) with a hydrolase (atrazine chlorohydrolase, AtzA) and found that each enzyme consists of 475 amino acids and differs by only 9 amino acids. Seffernick opined that their data suggest that the 9 amino acid differences between melamine deaminase and AtzA represent a short evolutionary pathway connecting enzymes catalyzing physiologically relevant deamination and dehalogenation reactions. As with Broun and Witkowski, Seffernick's data suggest that most changes in an enzyme's amino acid sequence (e.g., non-catalytic site amino acid residues) are not important in determining, or changing, its catalytic specificity. In Seffernick, there is no discussion regarding the merits or difficulties of protocols that screen for enzyme activity, e.g., screen for enzyme activity in a library of polypeptides expressed by a plurality of nucleic acid variants. It appears that Seffernick considered screening for enzyme activity a routine process.

Applicants respectfully aver that none of these references, individually or in their totality, are sufficient to rebut the instant application's presumption of enablement. None of these references are directed to whether, or not, screening a large number of nucleic acid variants would have constituted undue experimentation to one skilled in the art at the time of the invention. In fact,

PAGE 35/60 * RCVD AT 8/20/2004 9:23:39 PM [Eastern Daylight Time] * SVR:USPTO-EFXRF-1/1 * DNIS:8729306 * CSID:8587205125 * DURATION (mm-ss):25-38

because Broun, Witkowski and Seffernick's data suggest that most changes in an enzyme's amino acid sequence (e.g., non-catalytic site amino acid residues) are not important in determining, or changing, its catalytic specificity, these references support the idea that most changes in an enzyme's amino acid sequence will result in little or no effect on its specificity or activity, and that one of skill in the art could easily target a minimum number of residues to generate a limited number of enzyme variants to generate desired enzyme variants.

Accordingly, Applicants respectfully submit that the pending claims meet the written description and enablement requirements under 35 U.S.C. §112, first paragraph. In light of the above remarks, Applicants respectfully submit that amended claims are fully enabled by and described in the specification to overcome the rejection based upon 35 U.S.C. §112, first paragraph.

Issues under 35 U.S.C. §102(b)

The rejection of claims 1, 2, 4, 5, 7-14, 16-18, 47, 48, 75-87, 92 and 102 to 107, under 35 U.S.C. §102(b) as allegedly anticipated by Tachibana et al. (Database GenBank, US National Library of Medicine (Bethesda, MD, USA), No. D83793, TACHIBANA et al., 01 February 2000) (*Tachibana*), has been maintained.

The Office notes that the entire genome taught by *Tachibana* does not have 85% identity to the entire sequence of SEQ ID NO:125. The Office alleges that sequence taught by *Tachibana* comprises a region of 500 nucleotides having greater than 85% identity to a subsequence of SEQ ID NO:125, and a region of 100 nucleotides having greater than 90% identity to a subsequence of SEQ ID NO:125. The Office specifically indicates that a 510 nucleotide section of the gene of *Tachibana* has 86.5% identity to a specific region of SEQ ID NO:125. In addition, the Office specifically indicates that a 100 nucleotide section of the gene of *Tachibana* has 91% identity to a specific region of SEQ ID NO:125.

With regard to the amylase polypeptides of the present disclosure, the Office notes that sequence taught by *Tachibana* does not have 90% identity to the entire sequence of SEQ ID NO:126. The Office alleges that sequence taught by *Tachibana* comprises a region of 75 amino acids having greater than 90% identity to SEQ ID NO:126. The Office specifically indicates that a 96 amino acid section of the gene of *Tachibana* has 99% identity to a specific region of SEQ ID NO:126.

PAGE 36/60 * RCVD AT 8/20/2004 9:23:39 PM [Eastern Daylight Time] * SVR:USPTO-EFXRF-1/1 * DNIS:8729306 * CSID:8587205125 * DURATION (mm-ss):25-38

A claim is anticipated only if each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference." *Verdegaal Bros. v. Union Oil Co. of California*, 814 F.2d 628, 631, 2 USPQ2d 1051, 1053 (Fed. Cir. 1987); MPEP § 2131.

The present amendment addresses the outstanding claim rejections under 35 U.S.C. §102(b) over *Tachibana*. *Tachibana* does not teach a nucleic acid sequence having at least about 90% sequence identity to SEQ ID NO:125 over a region of at least about 200, 300, 400 or 500 or more consecutive residues; a nucleic acid sequence having at least about 97% sequence identity to SEQ ID NO:125 over a region of at least about 50, 75 or 100 or more consecutive residues; nor a nucleic acid sequence having at least about 95% sequence identity to SEQ ID NO:125 over a region of at least about 75, 100 or 150 or more consecutive residues (*see* Exhibit C, included herewith, which provides an alignment of the cited nucleotide sequence with that of SEQ ID NO:125).

In addition, *Tachibana* does not teach a polypeptide sequence having at least about 97% sequence identity to SEQ ID NO:126 over a region of at least about 150 consecutive residues; nor a polypeptide sequence having at least about 99% sequence identity to SEQ ID NO:126 over a region of at least about 75, 100 or 150 or more consecutive residues (*see* Exhibit D, included herewith, which provides an alignment of the cited amino acid sequence with that of SEQ ID NO:126).

Accordingly, as *Tachibana* fails to teach all of the elements of the amended claims, it may be removed as an anticipatory reference. Withdrawal of this rejection is respectfully requested.

Claims 17, 18, 47, 75-80, 87, 92 and 93 stand rejected under 35 U.S.C. §102(b) as allegedly anticipated by Lam et al. (WO 97/44361) (*Lam*).

The Office asserts that Lam teaches "a polynucleotide encoding the Archaebacterium AEPIII endoglucanase which comprises an oligonucleotide of 42 consecutive nucleotides . . . with 100% identity to nucleotides 262-303 of SEQ ID NO:125."

The present amendment addresses this rejection under 35 U.S.C. §102(b) over *Lam*. For example, *Lam* does not teach a nucleic acid sequence having at least about 90% sequence identity to SEQ ID NO:125 over a region of at least about 500 consecutive residues; a nucleic acid sequence having at least about 97% sequence identity to SEQ ID NO:125 over a region of at least

PAGE 37/60 * RCVD AT 8/20/2004 9:23:39 PM [Eastern Daylight Time] * SVR:USPTO-EFXRF-1/1 * DNIS:8729306 * CSID:8587205125 * DURATION (mm-ss):25-38

about 200 consecutive residues; a nucleic acid sequence having at least about 95% sequence identity to SEQ ID NO:125 over a region of at least about 300 consecutive residues; or, a nucleic acid sequence having at least about 99% sequence identity to SEQ ID NO:125 over a region of at least about 150 consecutive residues. Accordingly, as *Lam* fails to teach all of the elements of the present claims it may be removed as an anticipatory reference. Withdrawal of this rejection is respectfully requested.

Issues under 35 U.S.C. §103(a)

The rejection of claims 88 and 89 under 35 U.S.C. §103(a), as allegedly obvious over *Tachibana*, has been maintained

The present amendment to the claims rebuts this rejection under 35 U.S.C. §103(a). As discussed above, *Tachibana* fails to teach or suggest the nucleic acids of the amended claims. Accordingly, *Tachibana* does not teach or suggest all of the elements of the amended claims. Therefore, *Tachibana* does not render these claims obvious. Withdrawal of this rejection is respectfully requested.

PAGE 38/60 * RCVD AT 8/20/2004 9:23:39 PM [Eastern Daylight Time] * SVR:USPTO-EFXRF-1/1 * DNIS:8729306 * CSID:8587205125 * DURATION (mm-ss):25-38

CONCLUSION

In view of the foregoing amendment and remarks, it is believed that the Examiner can properly withdraw the rejection of the pending claims under 35 U.S.C. §112, first and second paragraphs, 35 U.S.C. §102 and 35 U.S.C. §103. Applicants believe all claims pending in this application are in condition for allowance. The issuance of a formal Notice of Allowance at an early date is respectfully requested.

As noted above, Applicants have requested a telephone conference with the undersigned representative to expedite prosecution of this application. After the Examiner has reviewed the instant response and amendment, please telephone the undersigned at 858 720 7943 or Gregory Einhorn at (858) 720-5133.

Applicants believe that no additional fees are necessitated by the present response and amendment. However, in the event any such fees are due, the Commissioner is hereby authorized to charge any such fees to Deposit Account No. 03-1952 referencing docket number 564462006100. Please credit any overpayment to this account.

Dated: August 20, 2004

Respectfully submitted,

By _____

David L. Devernoe
Registration No.: 50,128
MORRISON & FOERSTER LLP
3811 Valley Centre Drive, Suite 500
San Diego, California 92130
(858) 720-7943

sd-215892